11.30 – 12.00

LLC: Obinutuzumab e Rituximab prevede un sorpasso?

Prof. Antonio Cuneo, MD, PhD

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
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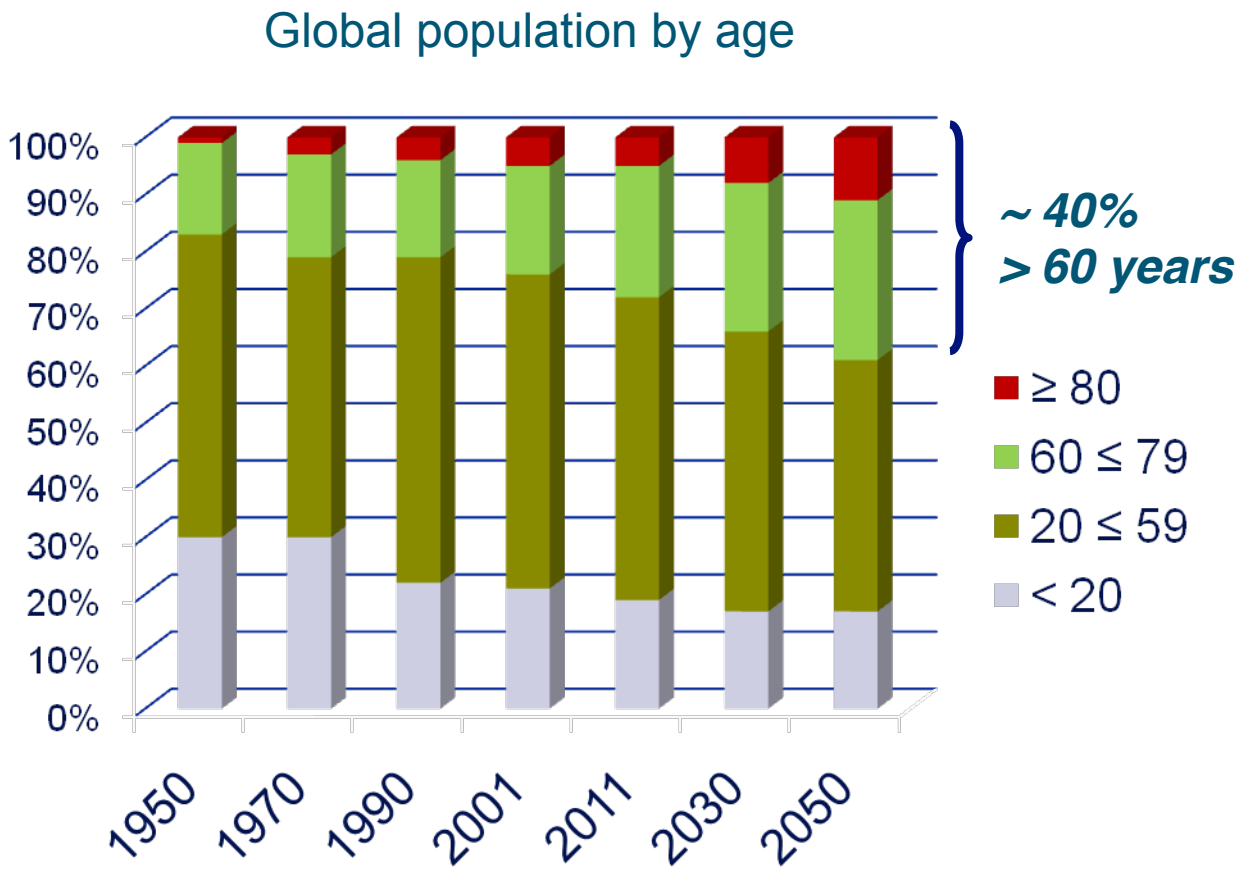
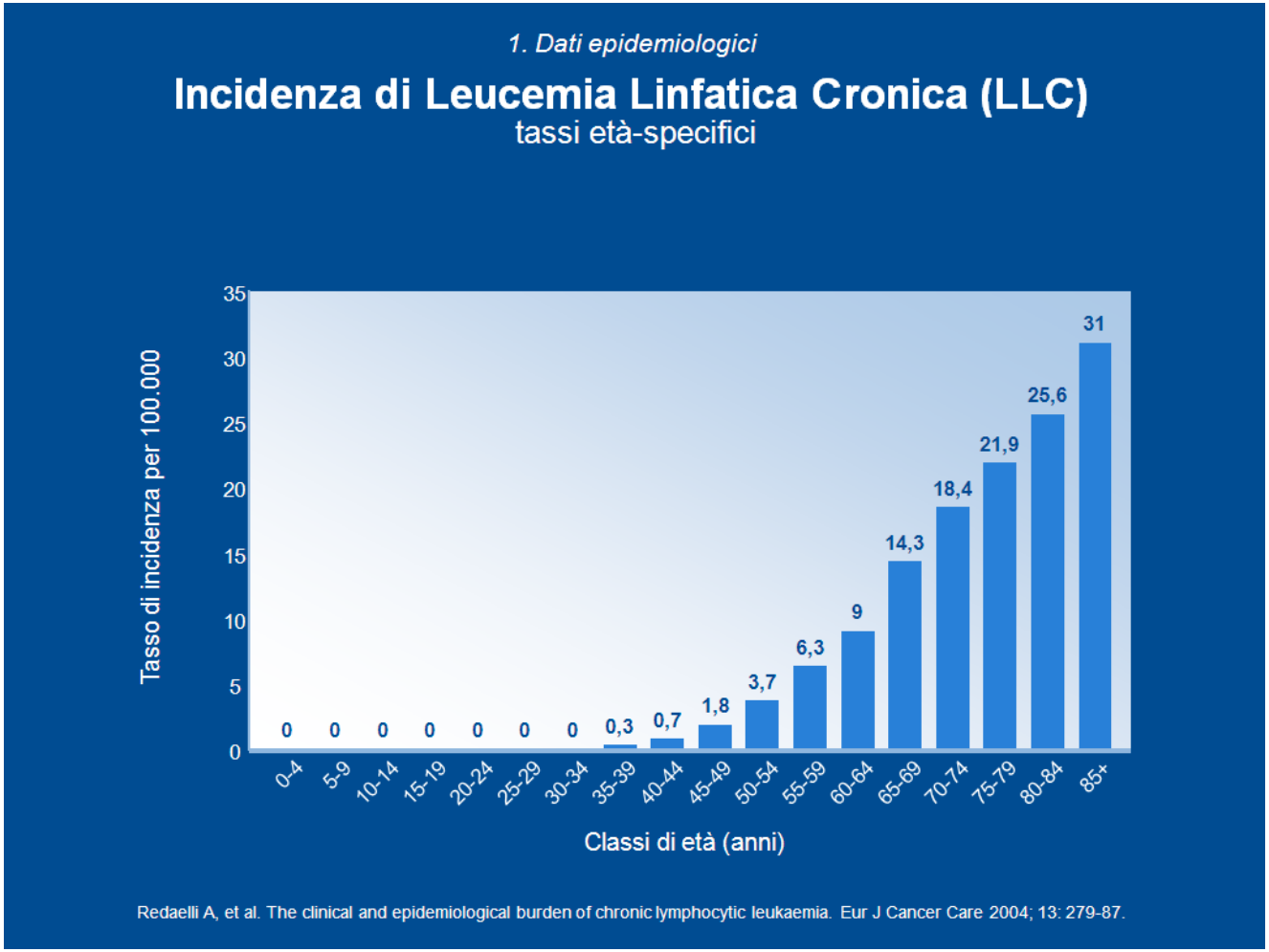
università di ferrara

Age distribution of EU population



Leucemia Linfatica Cronica nella vita reale

4.92 cases per 100,000/year in Europe (1. Sant, 2010)
14,620 new cases in 2015 in the U.S. (2. Siegel 2015)



1. Sant M, Allemani T, Tereanu C et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010; 3724-3734.

2. Siegel R L, Miller K D, Jemal A. Cancer Statistics, 2015CA Cancer J Clin 2015; 65:5–29.

Elderly CLL

Efficacy of chlorambucil + Rituximab as first line treatment

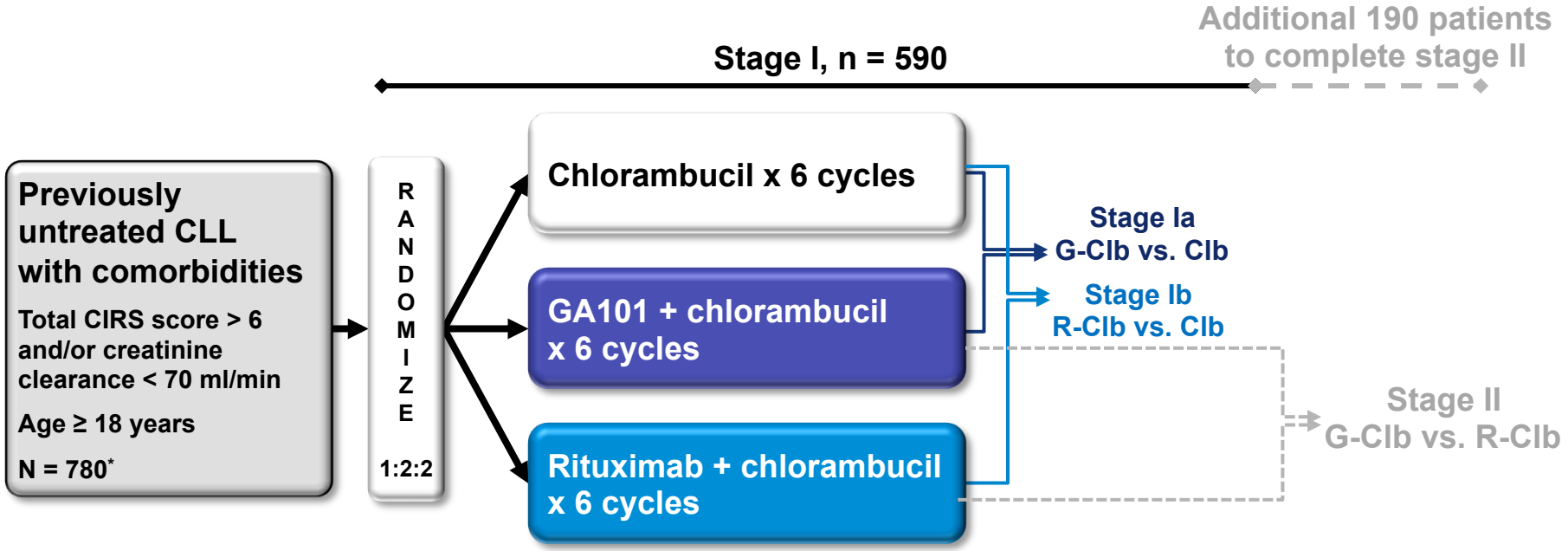
	No. of patients	Inclusion criteria	Median age	Total dose of Chlor	%CR/CRi	Median PFS (months)
	100	age18 years deemed non eligible to fluda	70	420 mg/sqm	10	23,5
	85	>65 60-65 non eligible to fluda	70	448 mg/sqm	19	34,7
	233	CIRS >6 Cr Clear<70	73	6 mg / Kg	8,3	15,7

UK: Hillmen P, JCO, Mar 17. [Epub ahead of print] 2014

Italy: Foà R on behalf of the GIMEMA group: Am J Hematol. 2014;89: 480-6

CLL11: Goede V, on behalf of CCLLSG: N Engl J Med. 2014;370:1101-10

CLL11 Phase III: Study design



GA101: 1,000 mg Days 1, 8, and 15 Cycle 1; Day 1 Cycles 2–6, every 28 days

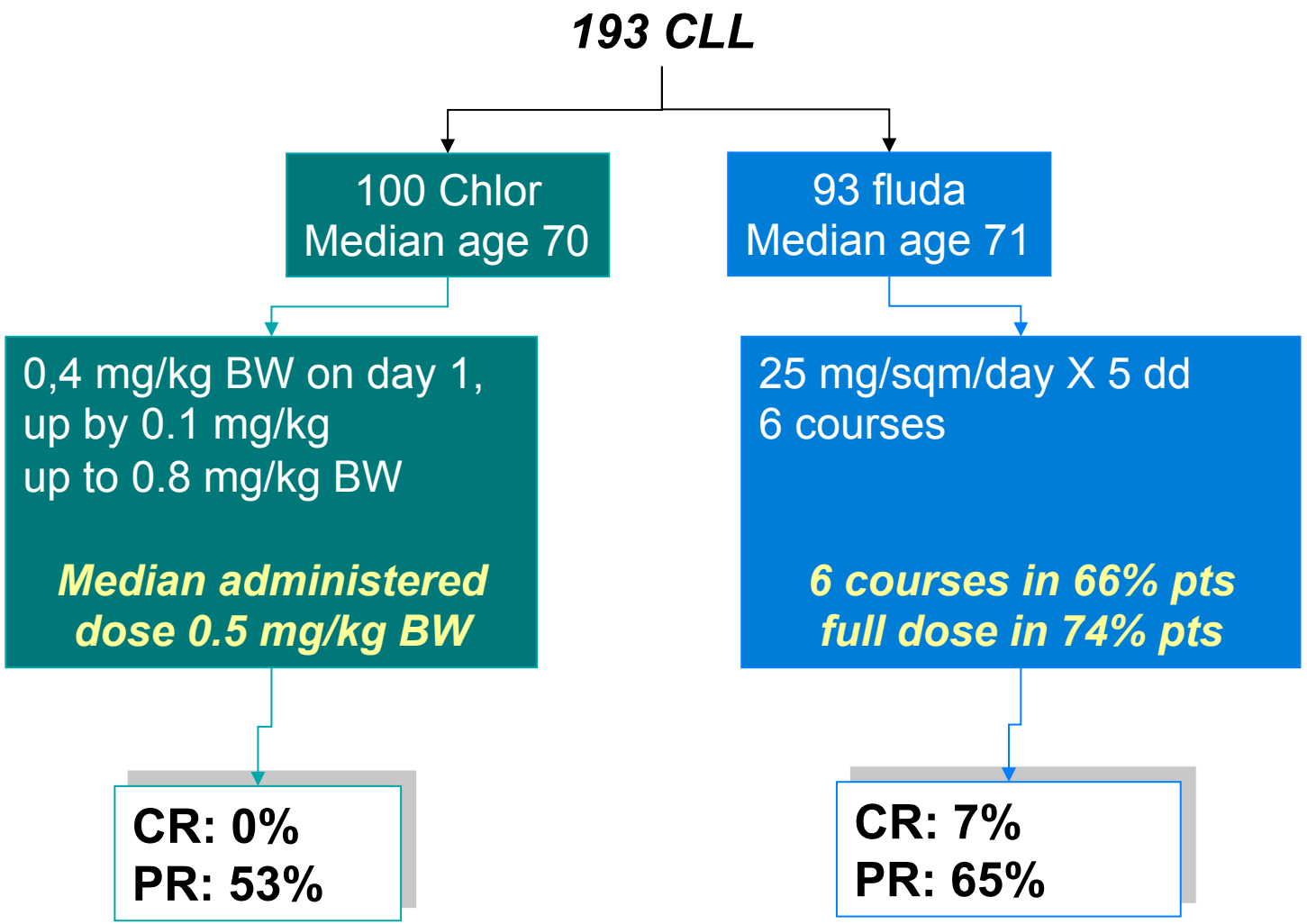
Rituximab: 375 mg/m^2 Day 1 Cycle 1, 500 mg/m^2 Day 1 Cycles 2–6, every 28 days

Clb: 0.5 mg/kg Day 1 and Day 15 Cycle 1–6, every 28 days

Goede V, *et al*. *J Clin Oncol* 2013: 31 suppl: Abstract 7004 (presentation update).
www.clinicaltrials.gov NCT01010061.

blood
2009 114: 3382-3391
Prepublished online July 15, 2009;
doi:10.1182/blood-2009-02-206185

First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia



Eichhorst, B. F. et al. Blood 2009;114:3382-3391

CLL11 stages Ia and Ib: Baseline disease characteristics

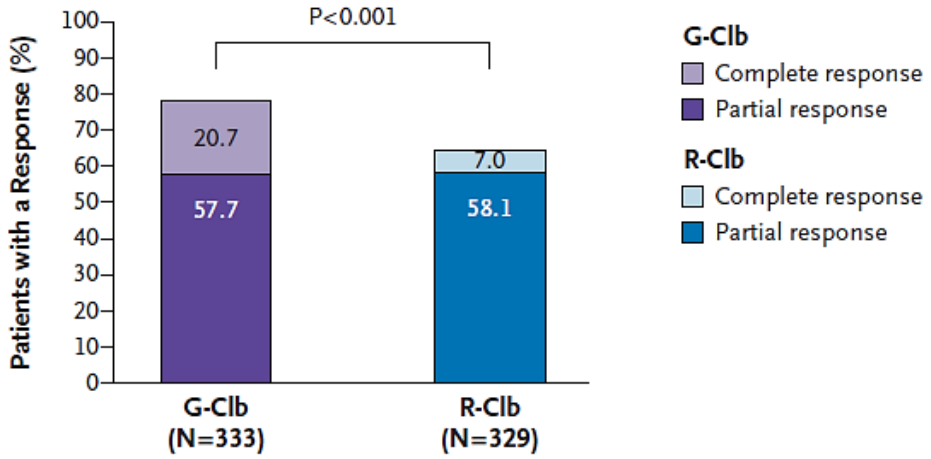
Characteristic	Patients, n (%)			
	Stage Ia		Stage Ib	
	Clb (n = 118)	G-Clb (n = 238)	Clb (n = 118)	R-Clb (n = 233)
Median age, years (range)	72 (43–87)	74 (39–88)	72 (43–87)	73 (40–90)
Male	64	59	64	64
Aged ≥ 75 years	37	45	37	45
CIRS score > 6	78	75	78	72
CrCl < 50 ml/min	21	29	21	24
Binet stage				
A	20	23	20	21
B	42	41	42	43
C	37	36	37	36
Circulating lymphocyte count ≥100 x10^9/l	37*	24*	37*	26*

* Circulating lymphocyte counts available for 116 patients in the Clb arm, 237 in the G-Clb arm, and 231 in the R-Clb arm. CrCl data available for 117/118 patients in the Clb arm. CrCl = creatinine clearance rate.

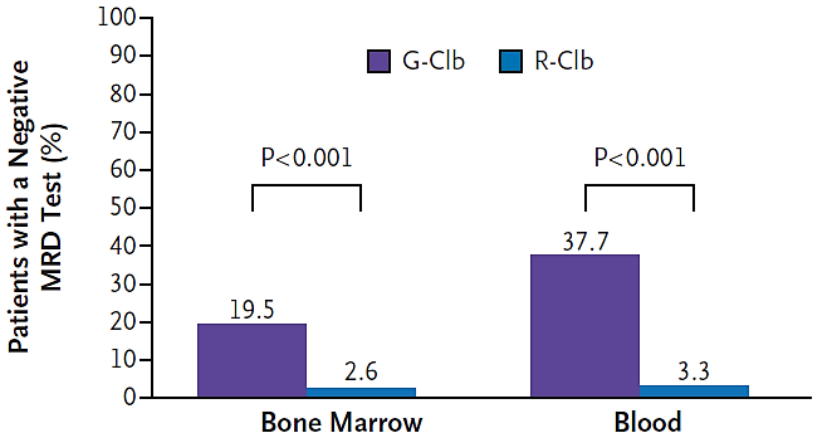
Adapted from Goede V, *et al*. *J Clin Oncol* 2013: 31 suppl: Abstract 7004 (presentation update).

CLL11 stage II (R-Clb vs. G-Clb)

CLL11 stage II Response Rate



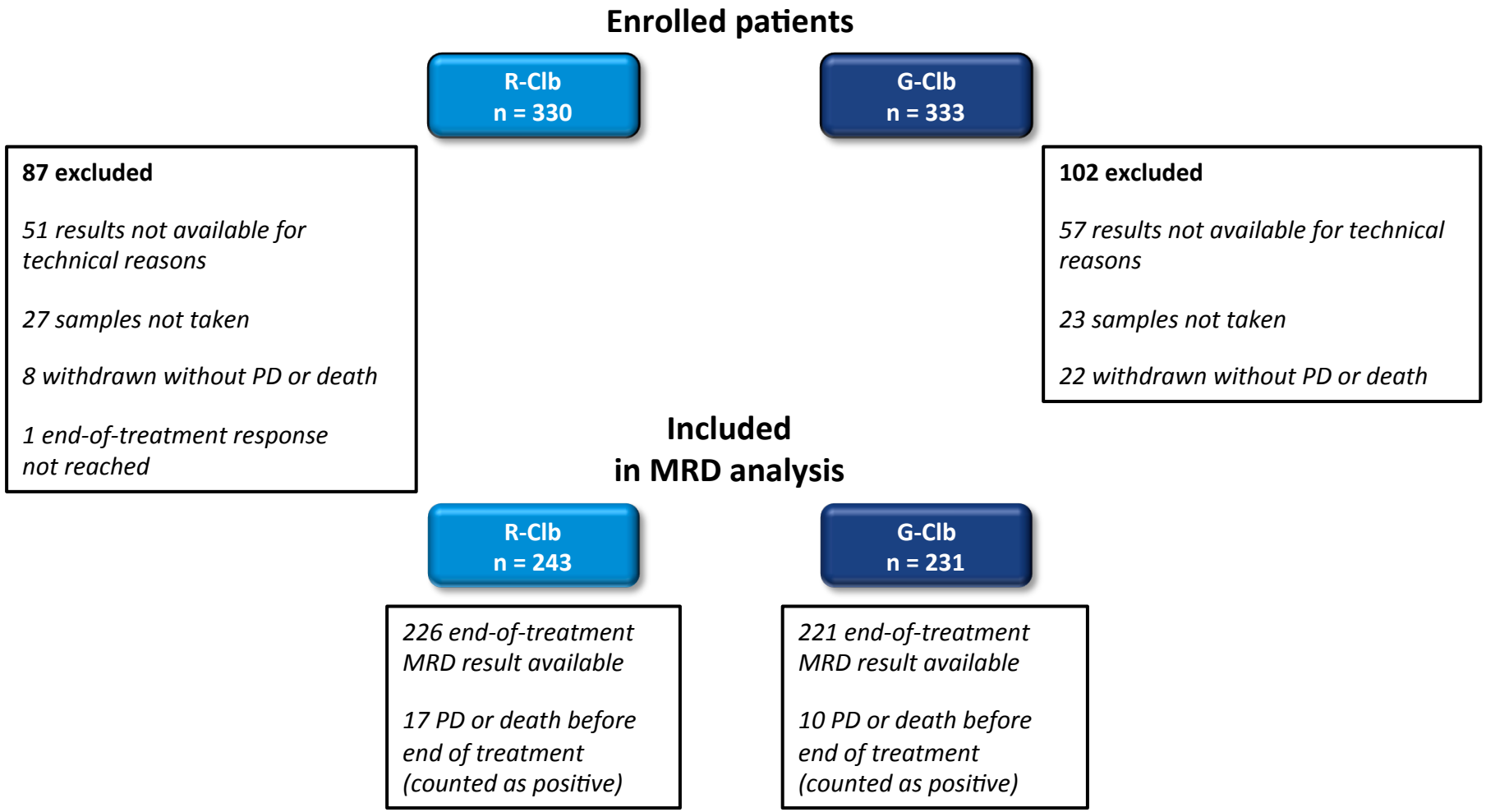
CLL11 stage II MDR negativity



No. of Patients	26/133	3/114	87/231	8/243

Goede V, et N Engl J Med 2014; 370:1101–1110

CLL11 stage II: Blood MRD sampling

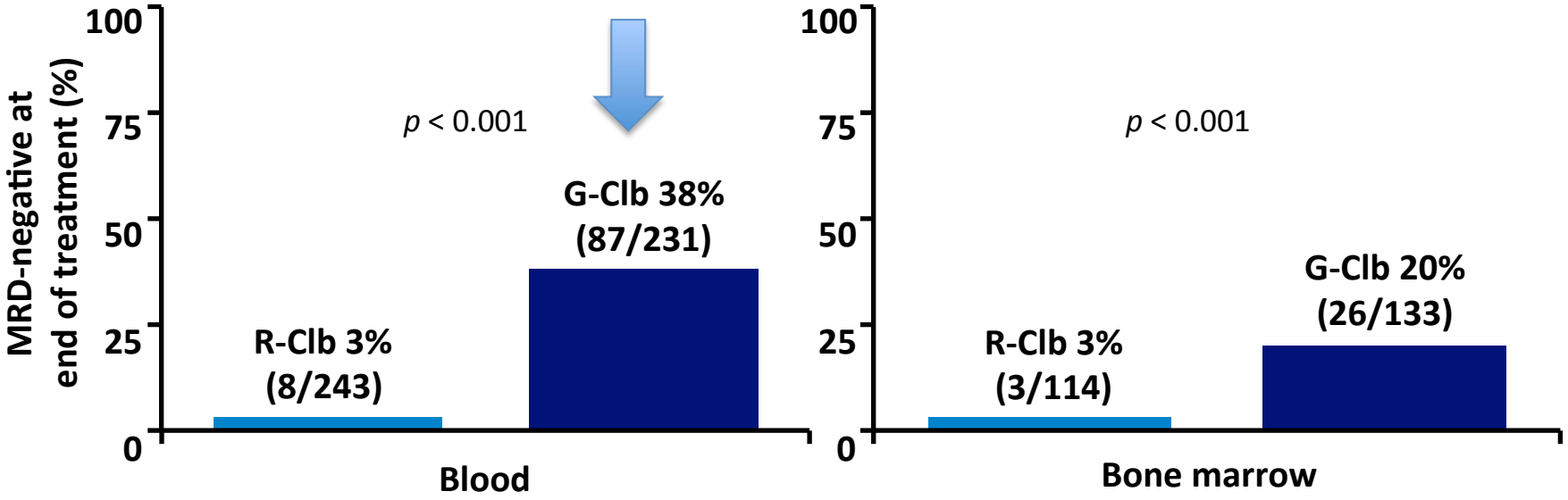


BM for MRD analysis was usually only taken from patients thought to be in CR

Goede V, *et al. N Engl J Med* 2014; 370:1101–1110.

CLL11 stage II: MRD at the end of treatment

- 38% of patients in the G-Clb arm were MRD-negative in peripheral blood and 20% in the BM at final response assessment, compared with 3% in the R-Clb arm

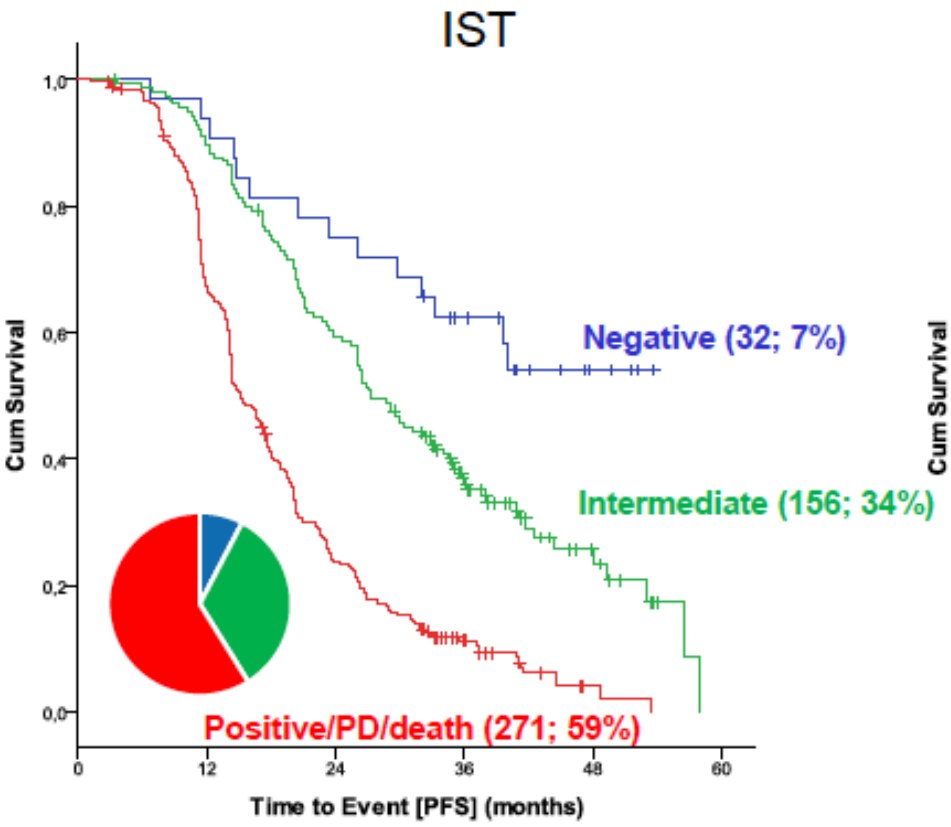


- MRD by ASO-RQ-PCR at final response assessment
- BM samples were usually only taken from patients thought to be in CR
- Patients who progressed or died prior to MRD measurement were counted as MRD-positive

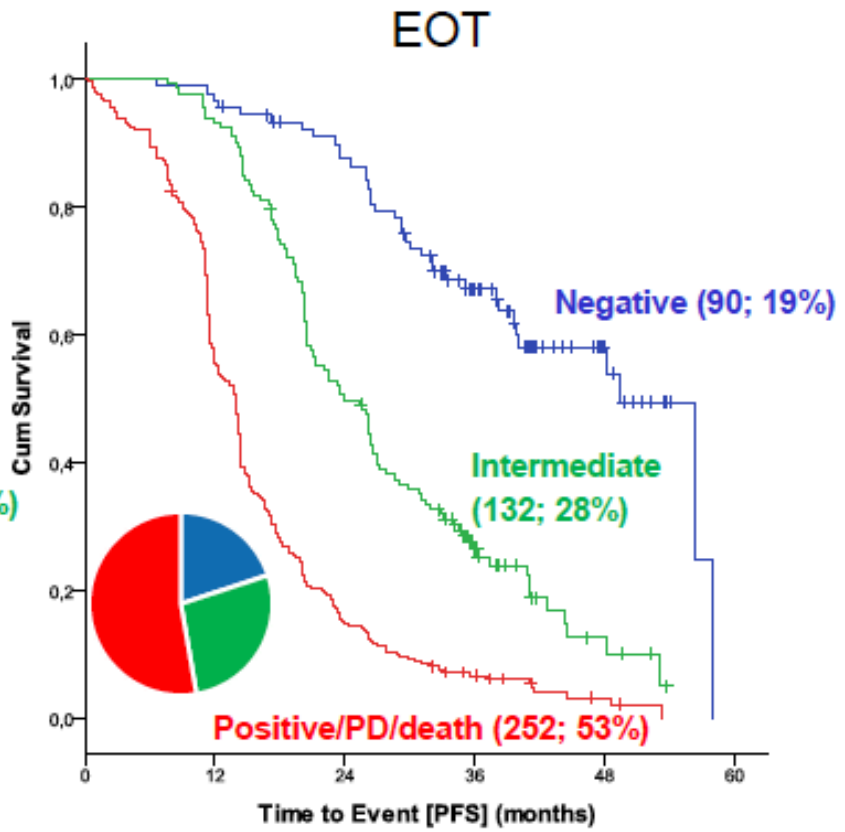
Goede V, *et al. N Engl J Med* 2014; 370:1101–1110.

PFS according to MRD status at IST and EOT

Stage 2 – peripheral blood



p < 0.001 (log-rank)

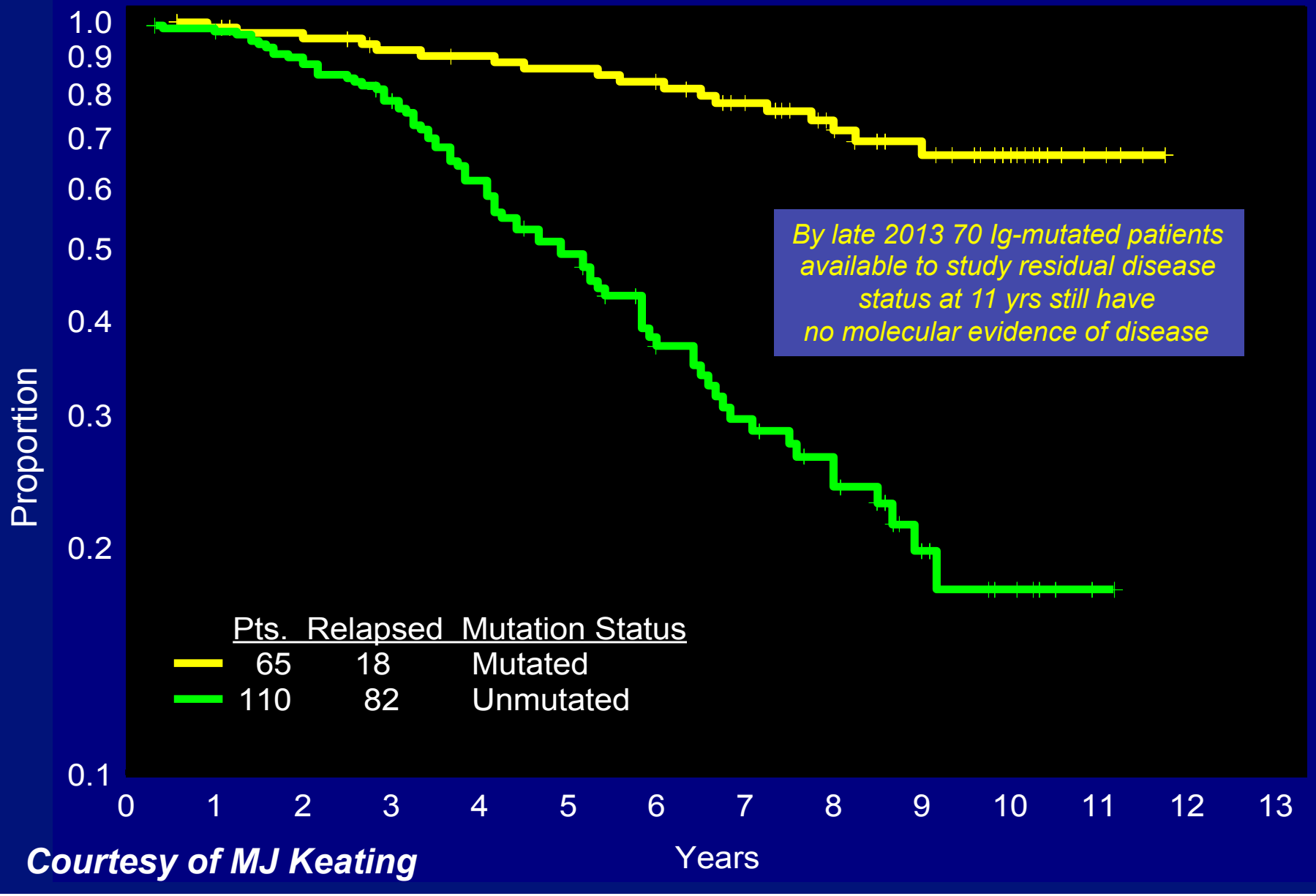


p < 0.001 (log-rank)

Data cut off: May 2015

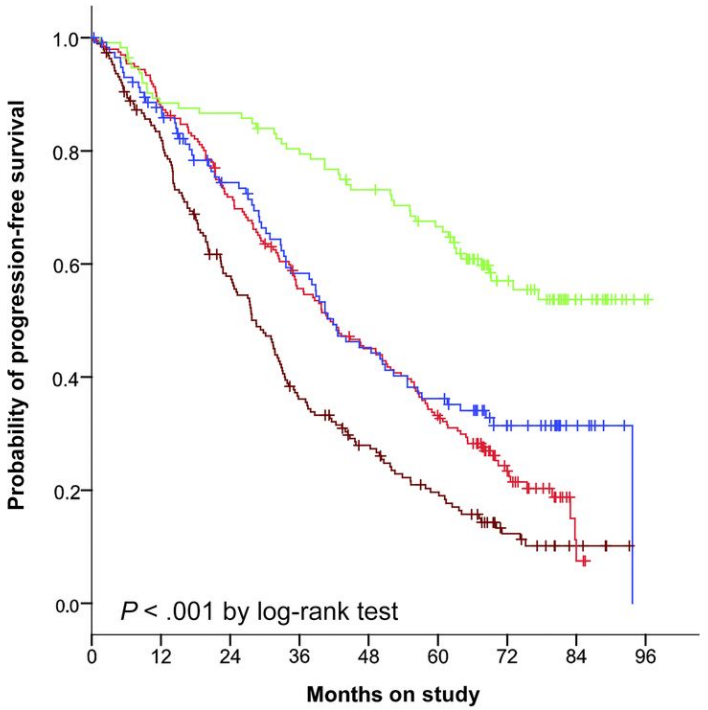
Importance of prognostic factors on the durability of response

FCR Time to Progression by Mutation Status FCR300 (logarithmic scale)



Courtesy of MJ Keating

Long term PFS with FCR (GCLLSG – CLL8)



66% progression free
at 5r yrs with plateau?

FCR *IGHV* MUT patients (N=113)

FC *IGHV* MUT patients (N=117)

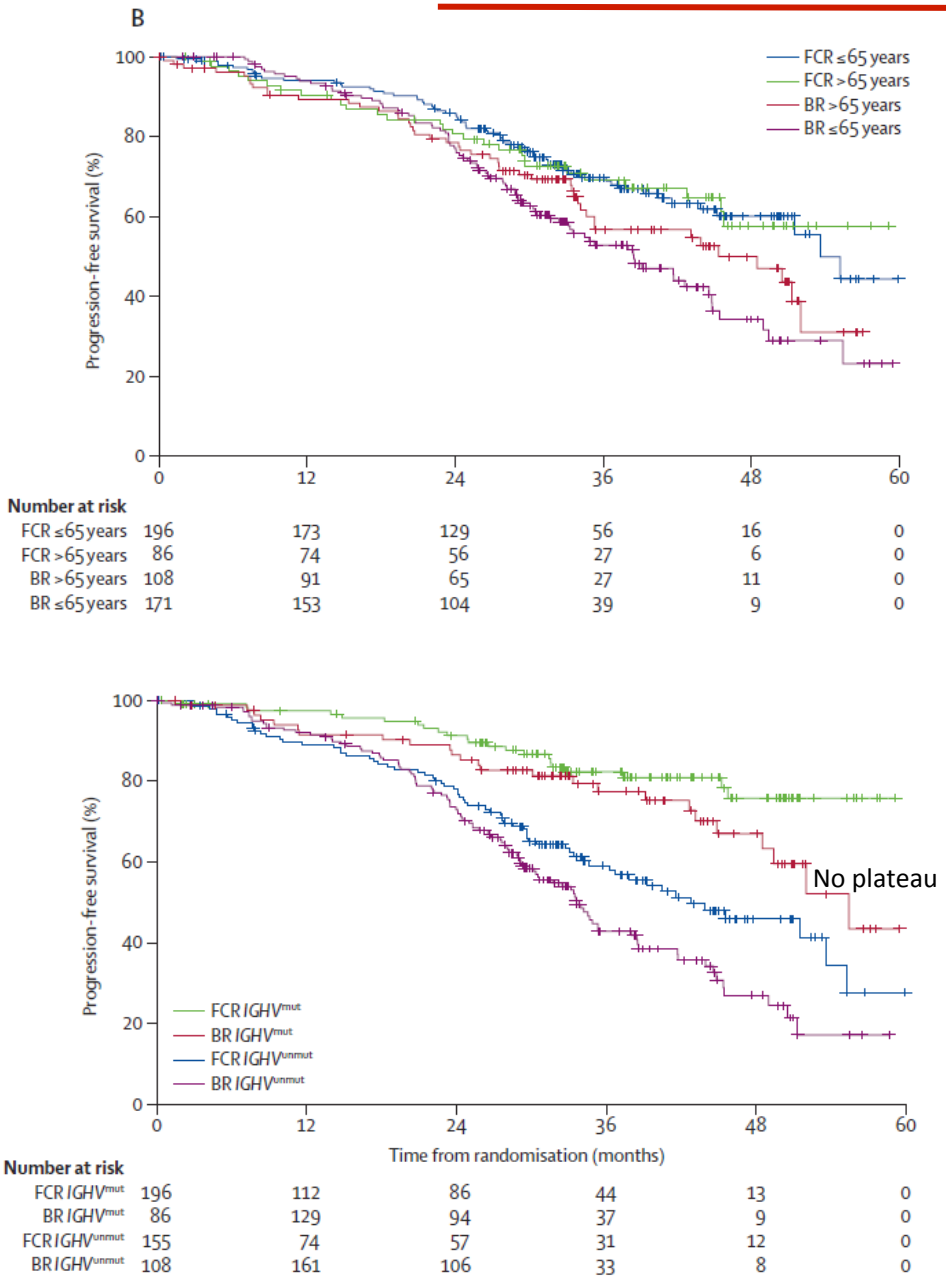
FCR *IGHV* UNM patients (N=197)

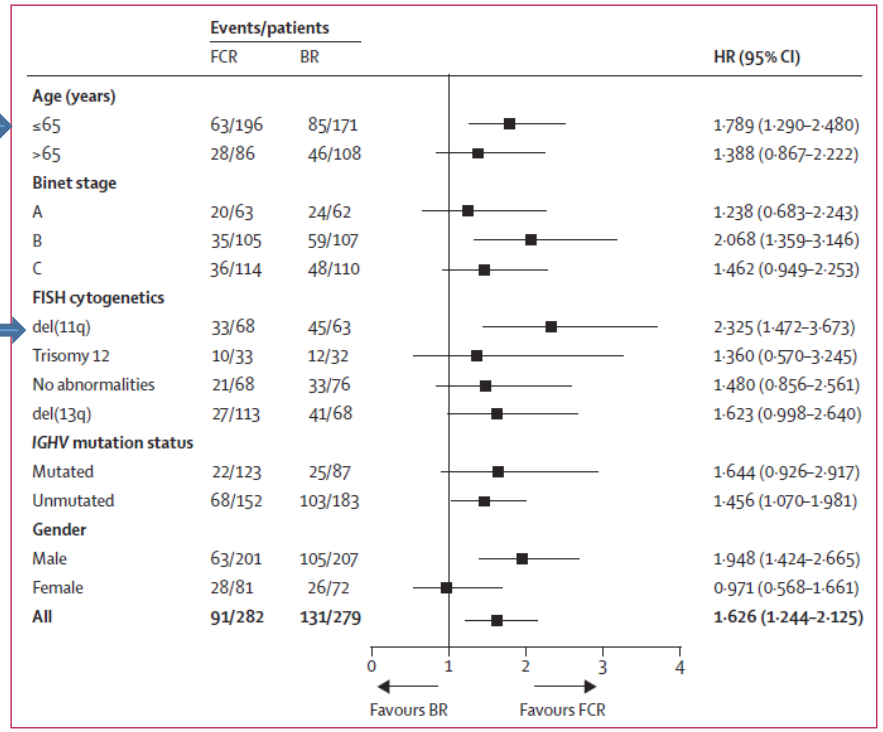
FC *IGHV* UNM patients (N=195)

Number at risk	0	12	24	36	48	60	72	84	96
FCR *IGHV* MUT	113	99	97	89	80	71	37	15	1
FC *IGHV* MUT	117	96	75	58	45	36	21	7	0
FCR *IGHV* UNM	197	173	140	106	85	61	25	2	0
FC *IGHV* UNM	195	153	105	65	45	30	12	4	0

Fischer K et al. Blood. 2016; 127:208-215

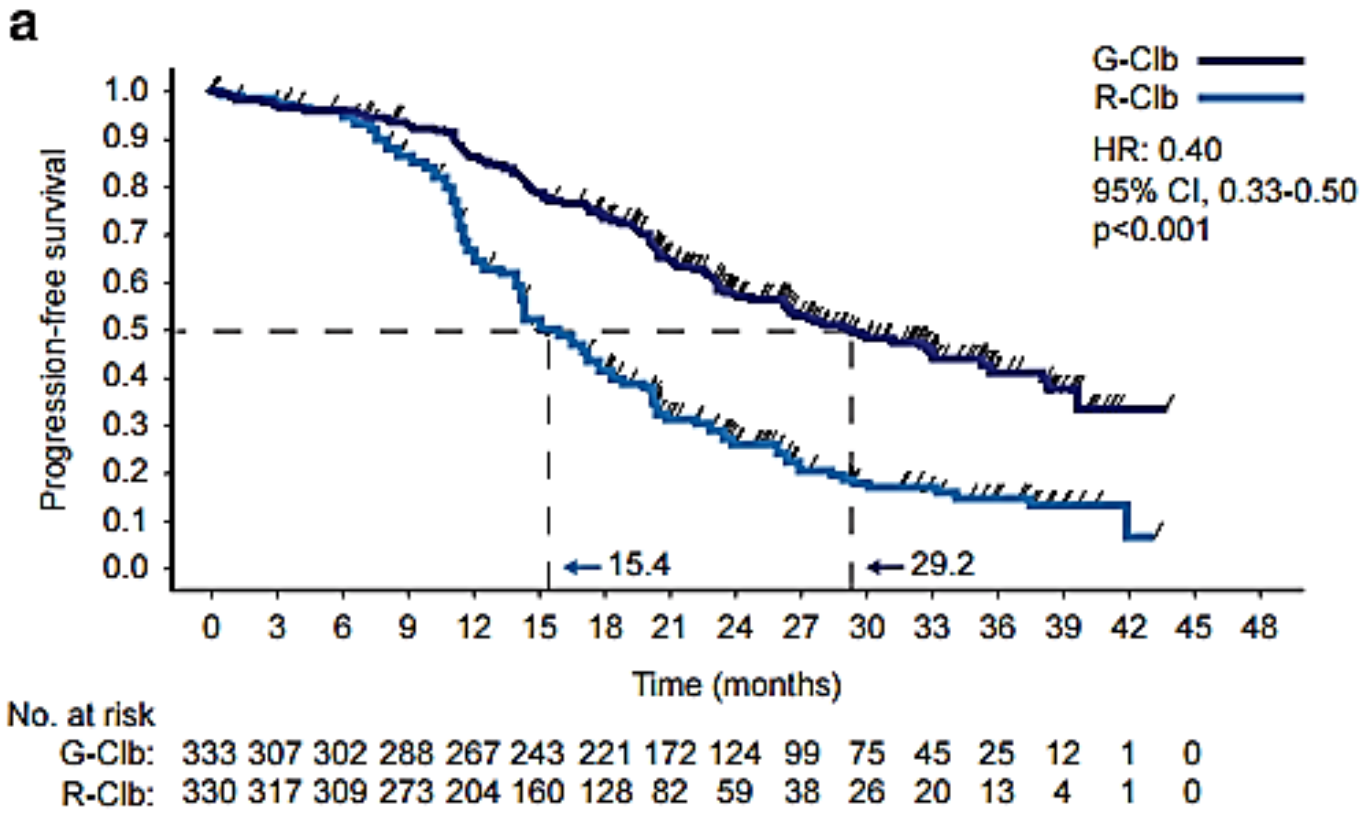
CLL10: PFS according to risk groups





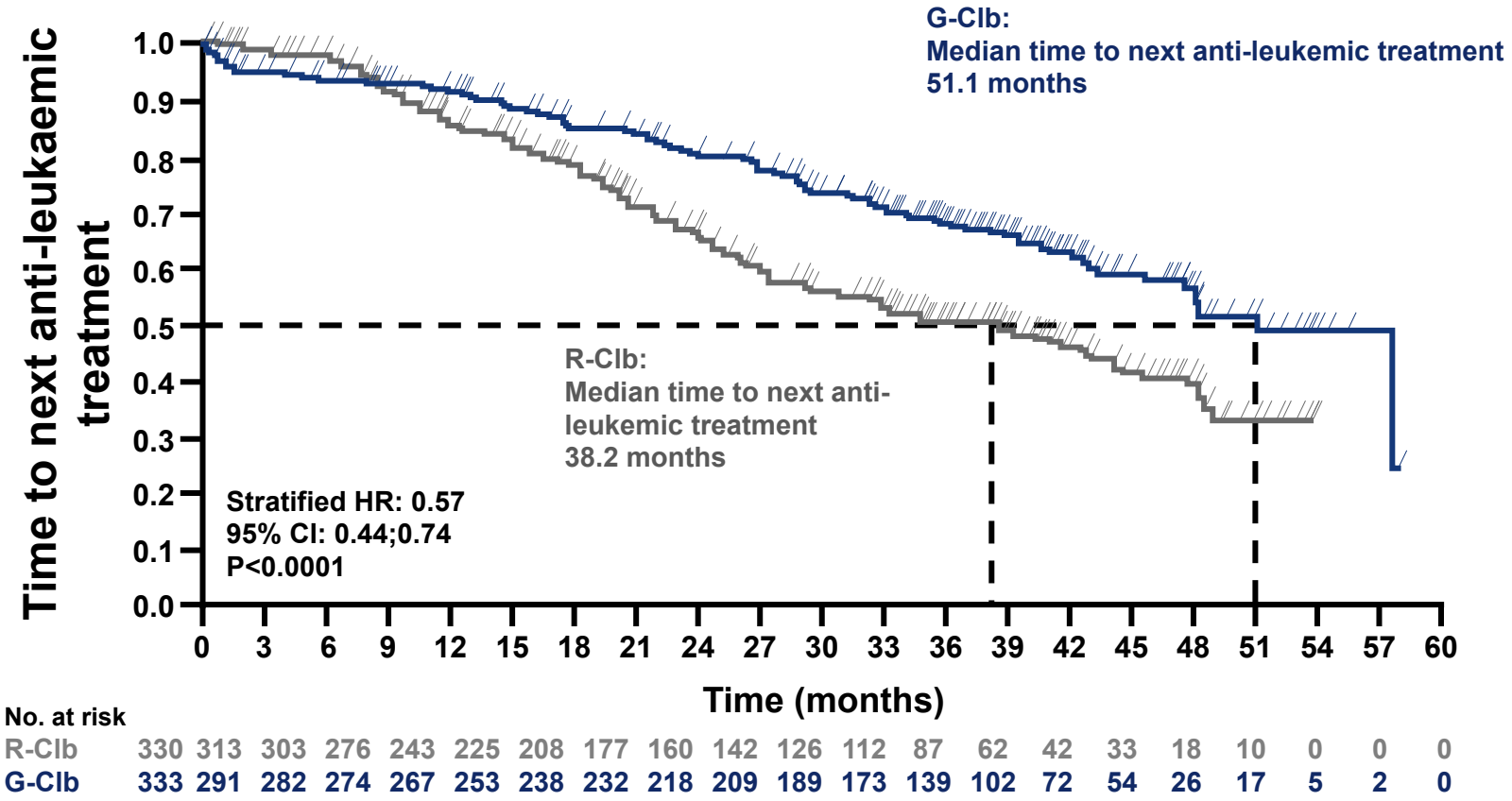
Eichhorst et al Lancet Oncol 2016;17:928-42

PFS: Update results of CLL11



Goede et al. Leukemia (2015) 29, 1602–1604; doi:10.1038/leu.2015.14; published online 17 February 2015

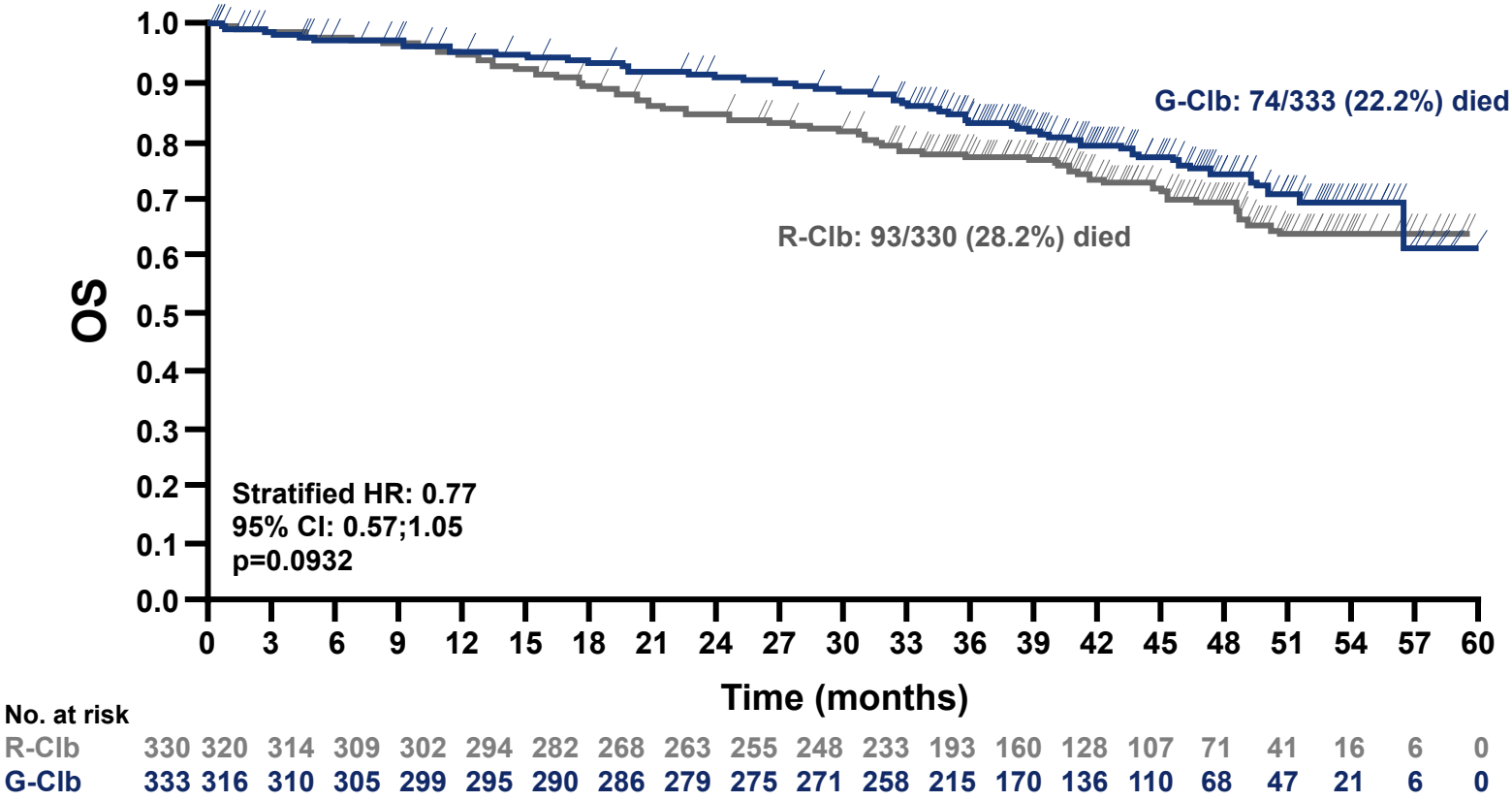
CLL11 stage II: Time to next anti-leukaemic treatment



CI, confidence interval; Clb, chlorambucil; CLL, chronic lymphocytic leukaemia;
G-Clb, Obinutuzumab + Clb; HR, hazard ratio; OS, overall survival; R-Clb, MabThera + Clb

Goede V, et al. Blood 2015;126:abstract 1733

CLL11 stage II: OS (May 2015 data cut-off)



CI, confidence interval; Clb, chlorambucil; CLL, chronic lymphocytic leukaemia;
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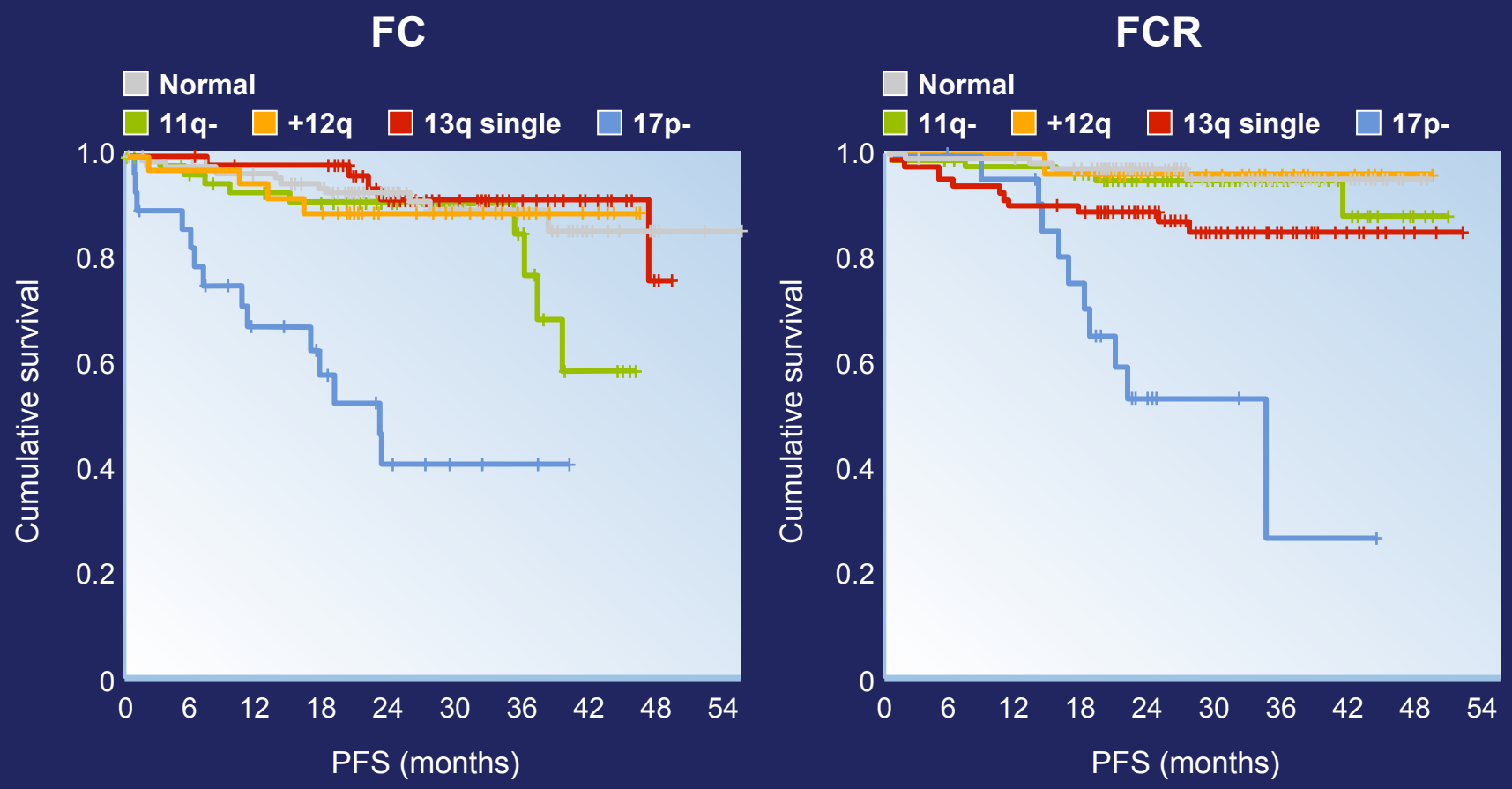
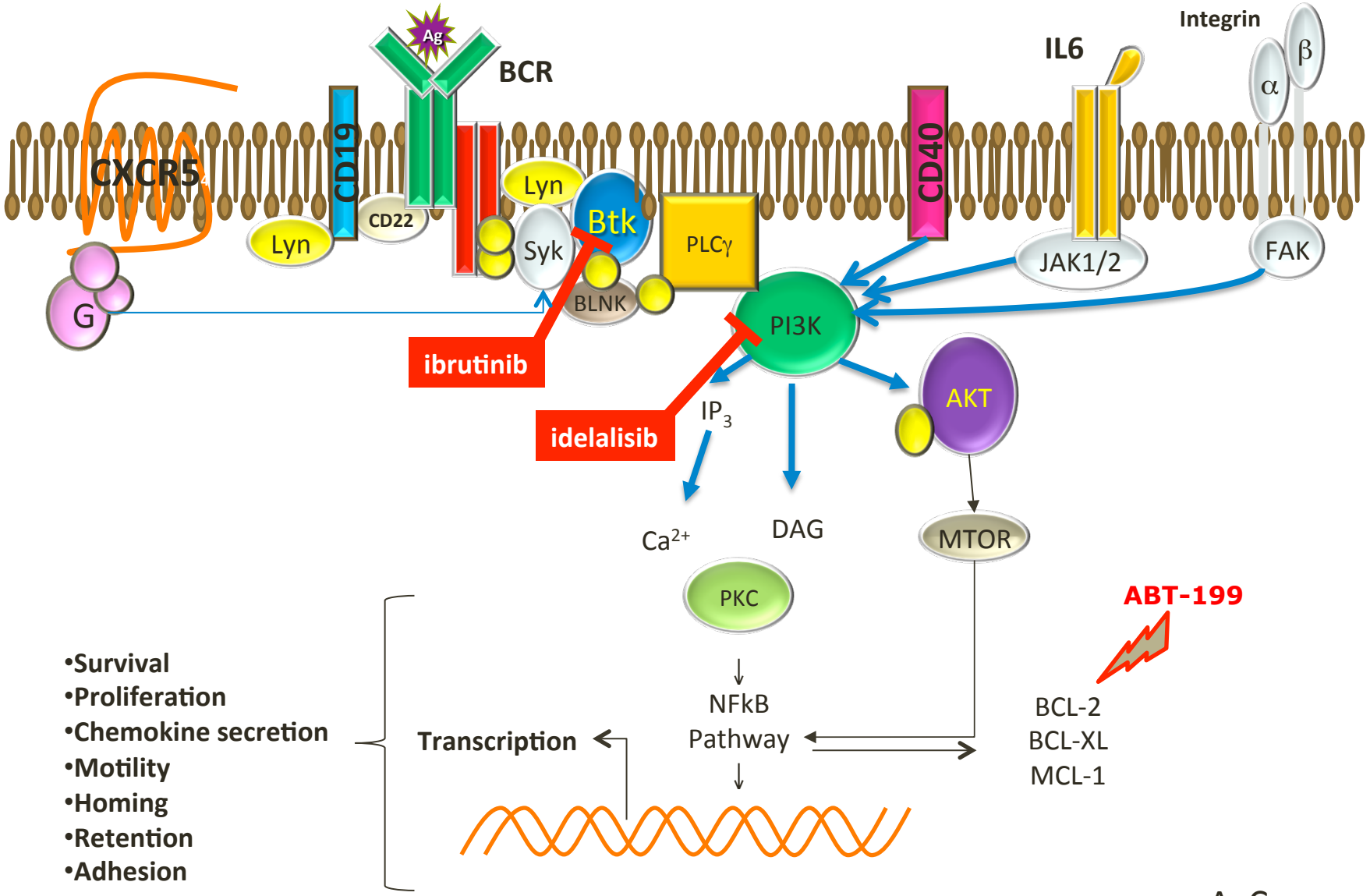
Goede V, et al. Blood 2015;126:abstract 1733

Addition of rituximab to fluda and CTX in CLL: a randomised, open-label, phase 3 trial
M Hallek et al Lancet 2010; 376: 1164–74

Poor outcome for 17p- patients



IBRUTINIB and IDELALISIB + R are approved in Europe for first line treatment of CLL with 17p-/TP53 mutations



A. Cuneo

Ibrutinib for previously untreated and relapsed or refractory CLL with TP53 aberrations: a phase 2, single-arm trial.

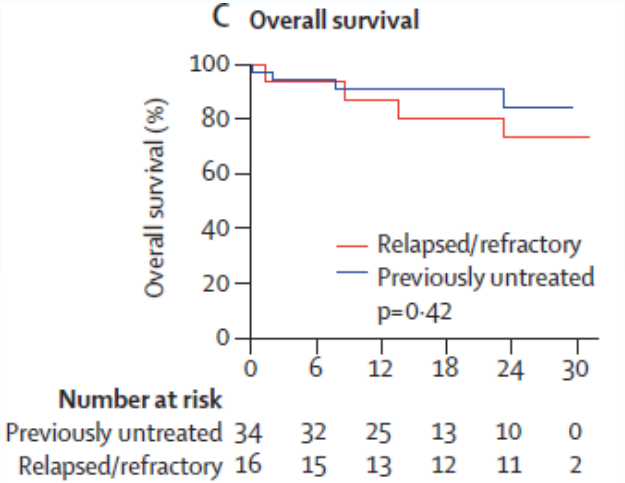
Response to treatment

	All evaluable patients (n=48)	Previously untreated patients (n=33)	Relapsed or refractory patients (n=15)
Response at 24 weeks			
Complete response	..	..	..
Partial response	24 (50%)	18 (55%)	6 (40%)
Partial response with lymphocytosis	20 (42%)	14 (42%)	6 (40%)
Stable disease	3 (6%)	..	3 (20%)
Progressive disease	1 (2%)	1 (3%)	..
Best response			
Complete response	5 (10%)	4 (12%)	1 (7%)
Partial response	32 (67%)	23 (70%)	9 (60%)
Partial response with lymphocytosis	8 (17%)	5 (15%)	3 (20%)
Stable disease	2 (4%)	..	2 (13%)
Progressive disease	1 (2%)	1 (3%)	

Farooqui MZ et al, Lancet Oncol. 2015 Feb;16(2):169-76

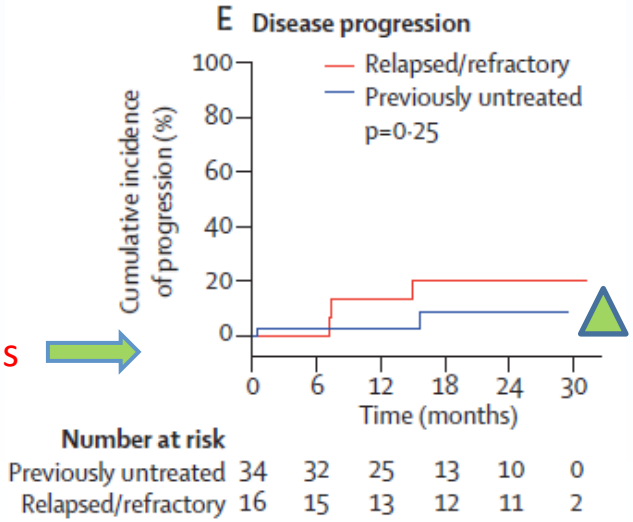
Ibrutinib monotherapy in First-Line CLL: Impact of del(17p) on treatment response (Phase II)

Overall survival in subgroups by treatment history



Cumulative incidence of disease progression by treatment history

Median follow-up for the previously untreated cohort was 15 months

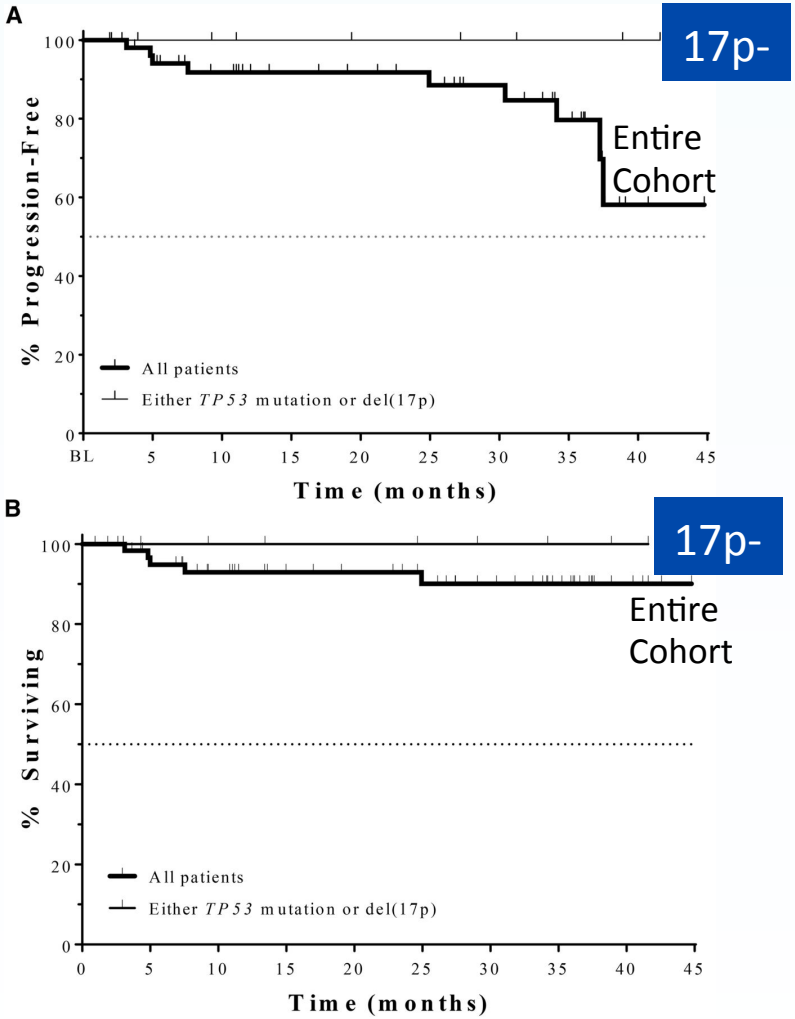


Farooqui M, *et al. Lancet Oncol* 2015;16:169–176.

Idelalisib + Rituximab first-line therapy in the elderly

Patients (%)	Idelalisib (n = 64) with 17p-: 9 patients
Treatment response[1]	
ORR	97*
CR	19
PR	78
Safety[1]	
Diarrhea/colitis (Grade 3)	42
Pneumonia (Grade 3)	19
AST/ALT (Grade 3)	23

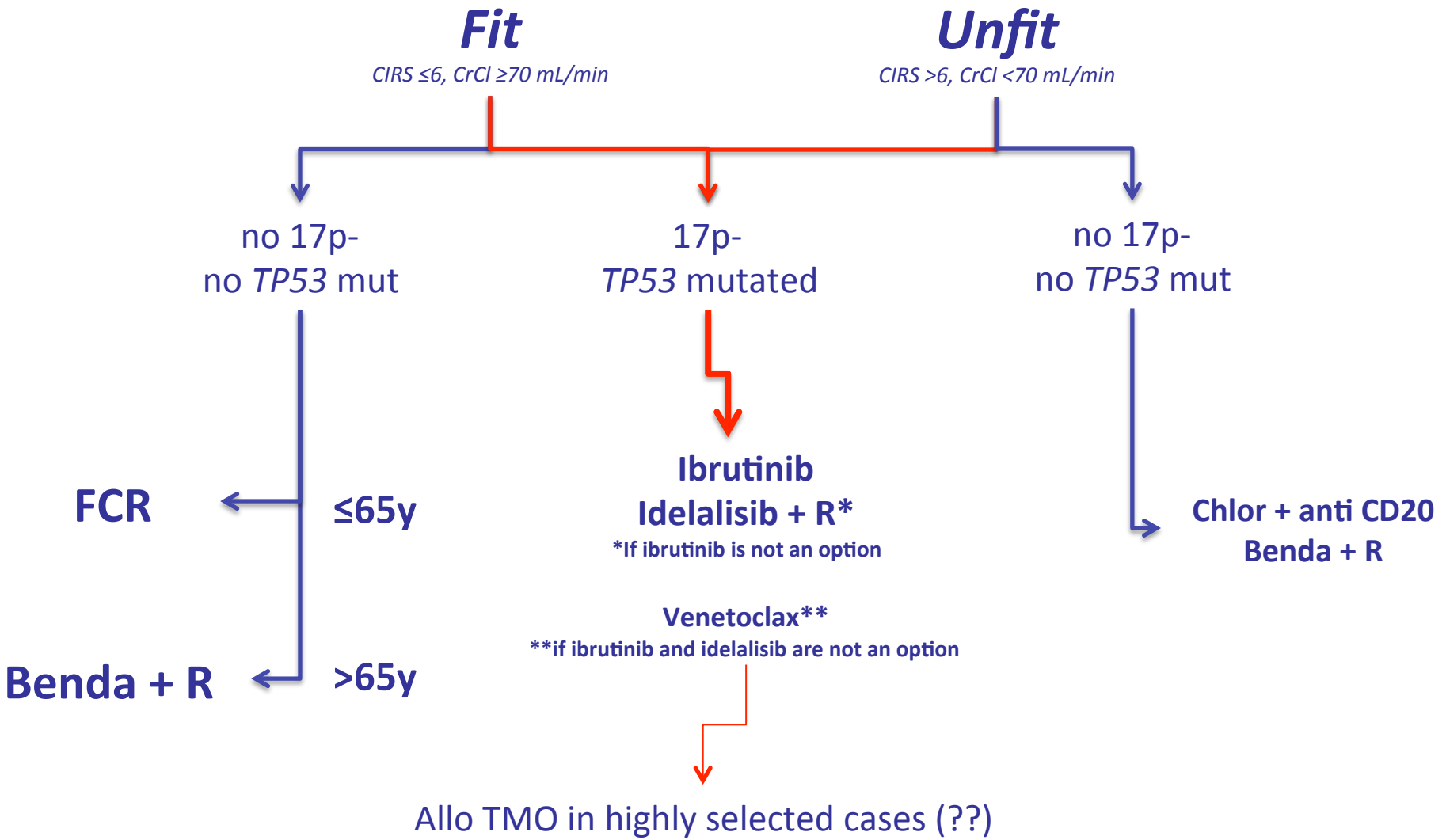
- Median age: **71 years** (65–90 years)[1]
- Median time to response: 1.9 months[1]
- Median time on idelalisib: **22.9 months**[1]
- Completed 48 weeks of therapy: 67%, most discontinuations due to AEs[1]



AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase.
* 3% of patients unevaluable.[1]

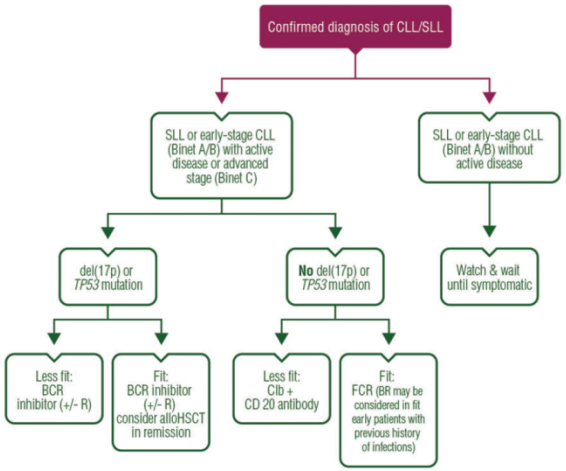
1. O'Brien S, *et al.* ASH 2014. Abstract 1994; 2. Lamanna N, *et al.* iwCLL 2013; 3. Zydelig SmPC, October 2014.

Options for first line treatment in CLL

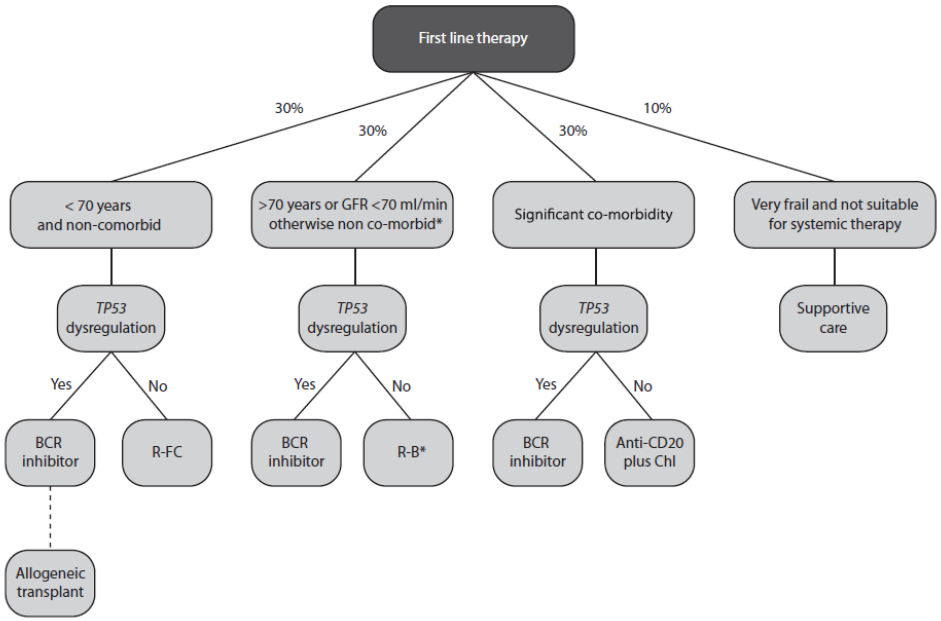


Cuneo A, personal view,
adapted from NCCN 2015; Hallek M. Am J Hematolol 2015; Stilgenbauer S Education book ASCO 2015

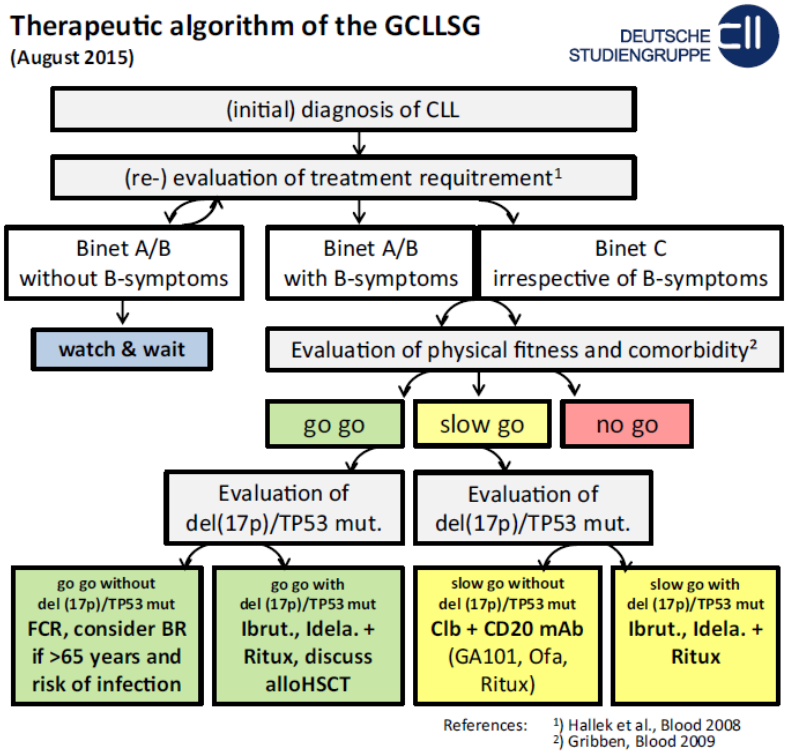
Recent guidelines and experts' opinion



Eichhorst et al, Annals Oncol 2015



Routledge et al; Review article - BJH 2016



Cramer et al EJH 2016

Why wasn't obinutuzumab uniformly recommended as the preferred choice?

Issues with CLL11 trial	Reason	
	Favors rituximab	Favors obinutuzumab
Dosage of chlorambucil	lower than commonly used	The dosage was the median tolerated dose in a previous trial
PFS	similar as compared with other trials using higher doses of chlor with R	The patient population of these trials is different (median age, comorbidities)
Endopoint	Overall survival in not better	PFS and TTNT are important endopints
Infusion reactions	More frequent with obinutuzumab (7% discontinuiation)	Manageable with pre-medication
Other combination	Bendamustine and rituximab may be at least as effective	There are few data with this combination in unfit/elderly patient

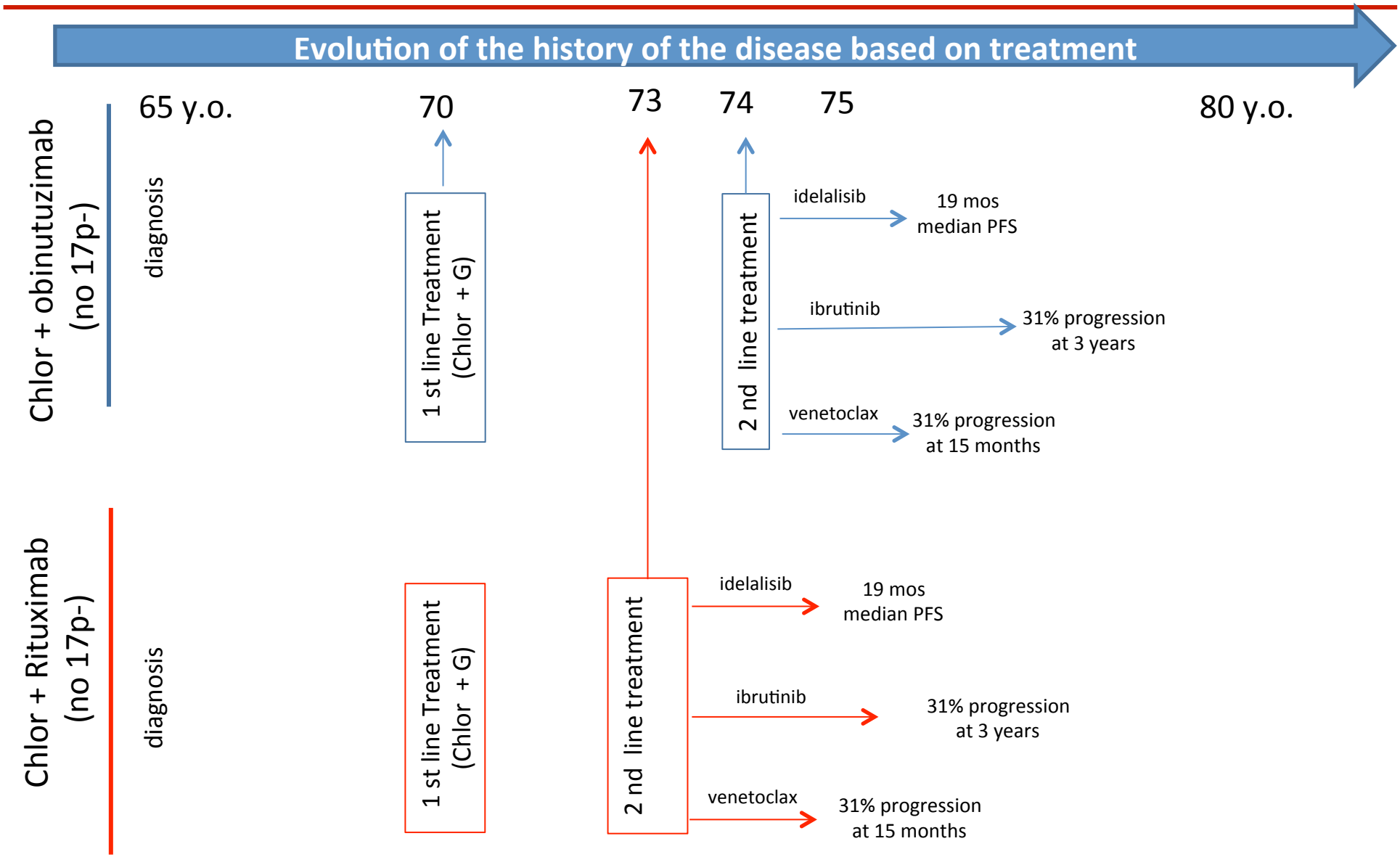
Considerations on the treatment algorithm

Assumptions	years	Reference and comments
Median age at diagnosis - Unfit	65	1,2,3,4 The very elderly and the frail patient are excluded TP53 disruption excluded
Median time to first treatment IGHV mutated IGHV unmutated	5 8 2	5,6 5,6
Median time to next treatment • Chlor + Obinutuzumab Chlor + rituximab	 4 3	 3 3

1)Eicchorst Lancet Oncol 2016; 2) Foà, Am J Hematol 2014; 3) Goede NEJM, 2014; 4) Hillmen, JCO 2015; 5) Shanafelt Cancer 2010, 6) Martinelli MJH 2016

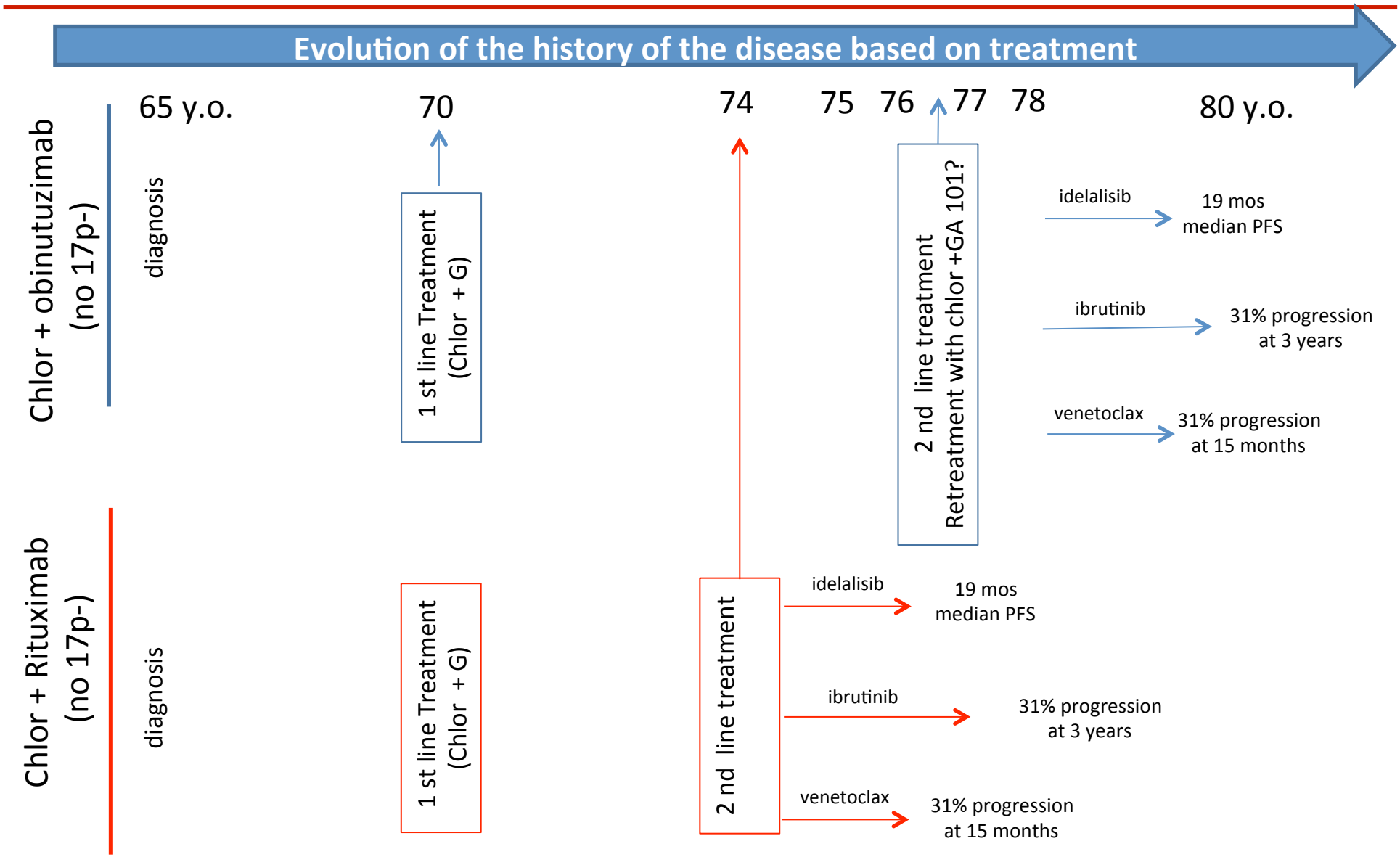
Some assumptions on the history of CLL treatment with chlorambucuil and anti CD20

(personal view: the typical patient, excluding the frail one)



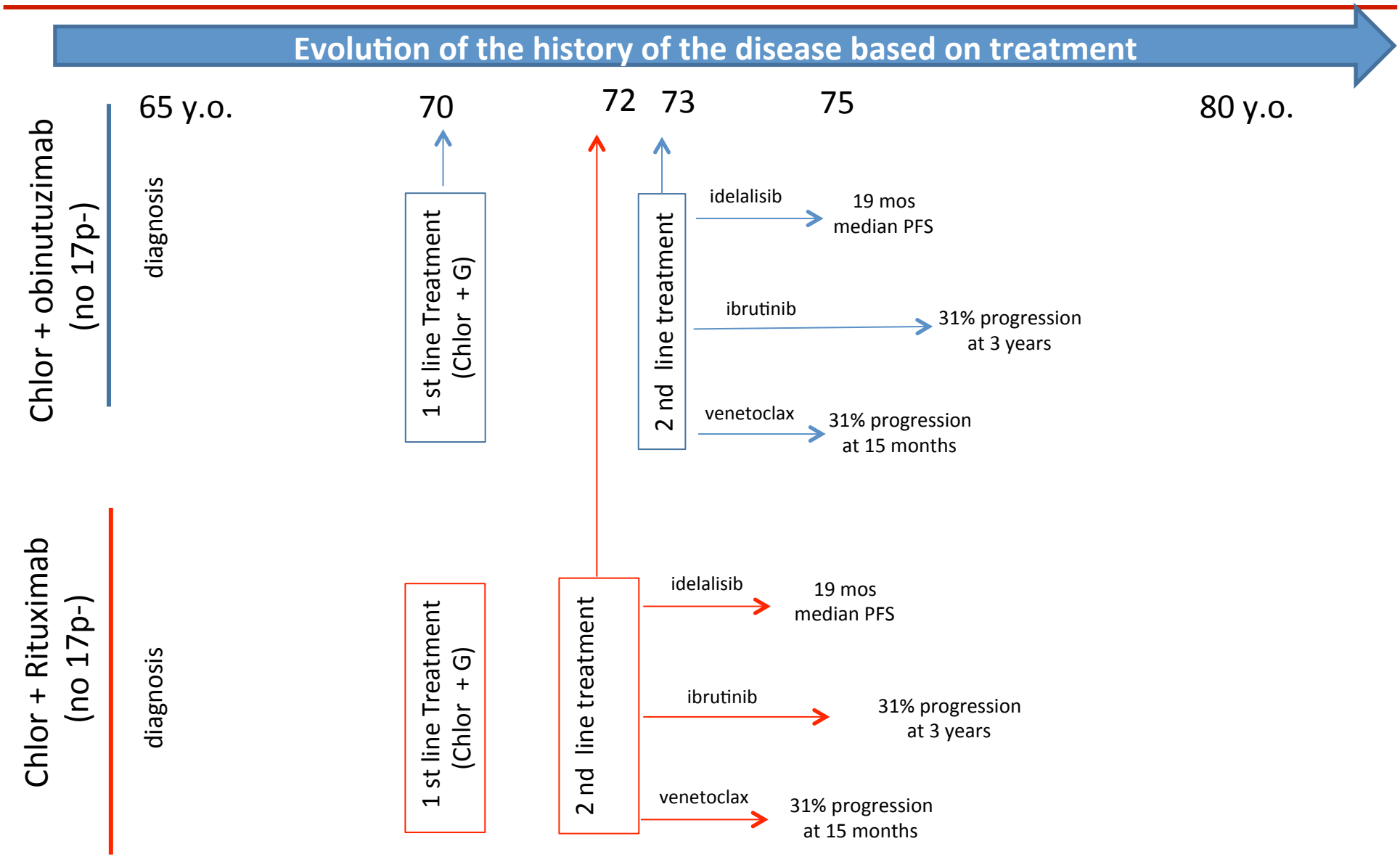
Some assumptions on the history of CLL treatment with chlorambucuil and anti CD20

(The patients with favourable risk: IGHV mutated assuming 6-7 years TTNT with obinutuzumab)



Some assumptions on the history of CLL treatment with chlorambucuil and anti CD20

(The patients with unfavourable risk: IGHV unmutated assuming 2-3 yrs TTNT)

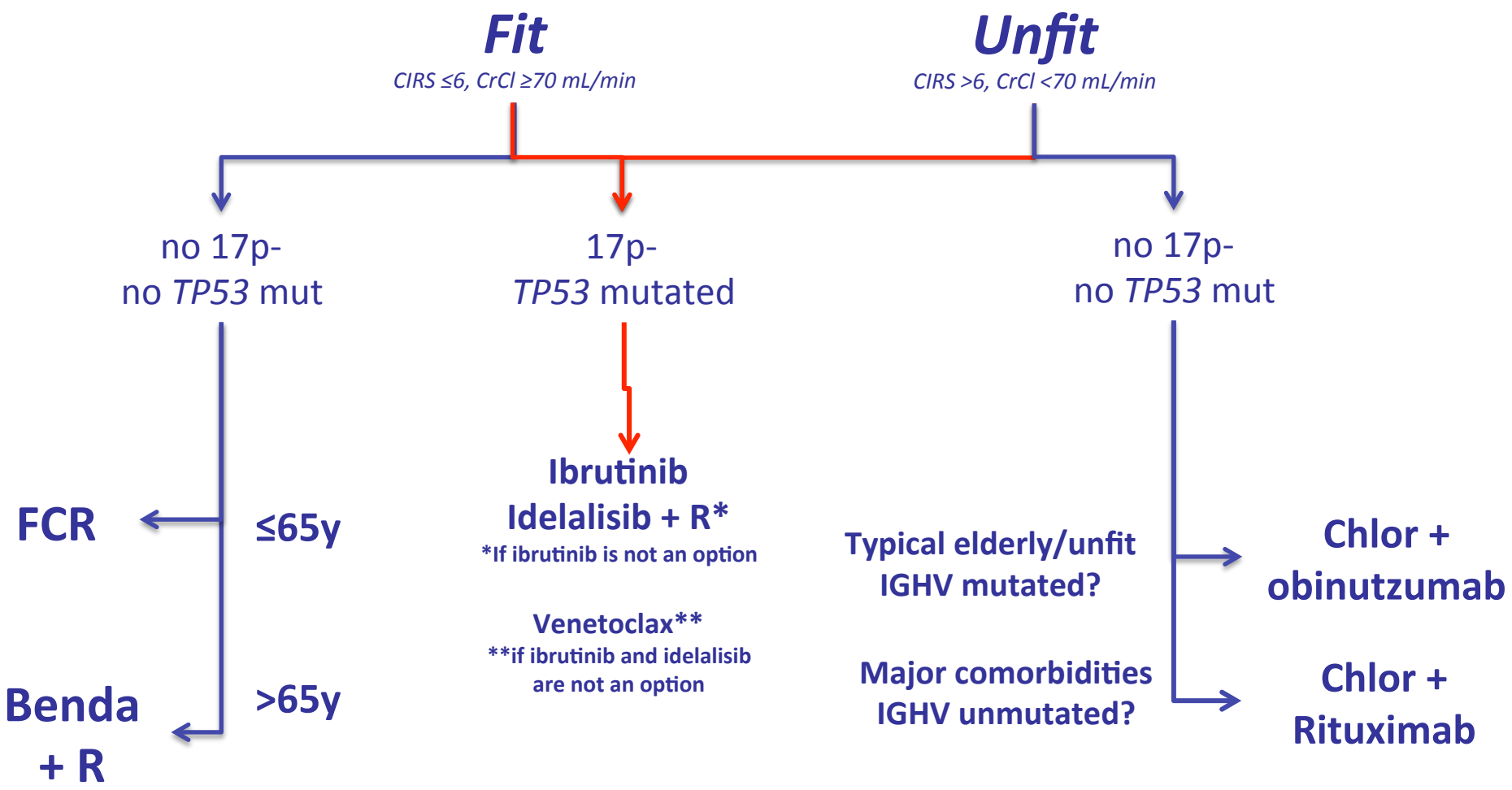


Obinutuzumab or rituximab with chlorambucil in the elderly/unfit?

Some considerations

- Time to next treatment is an important endopint in the elderly patient
- Infusion reactions occur more frequently with obinutuzumab (most of them during the first cycle)
- Infusion reactions are manageable
- There are favourable risk group (i.e. IGHV mutated) which may achieve MRD- status and prolonged PFS (waiting for the CLL11 data)

Options for first line treatment in CLL



Cuneo A, personal view,
adapted from NCCN 2015; Hallek M. Am J Hematolol 2015; Stilgenbauer S Education book ASCO 2015